

consisting of VYAK; VWAK; VEAk; FEAK; VAK; WAK; YAK; FAK; YEK; ELSA; DLYV; and KEASV.

109. A method for ameliorating unwanted immune responses by administering to a subject in
5 need thereof an effective amount of random copolymer wherein said random copolymer
comprises a plurality of amino acid residues selected from:
- (1) hydrophobic, aliphatic residues (leucine, isoleucine, valine, methionine);
 - (2) acidic residues (aspartic acid, glutamic acid);
 - (3) small hydrophilic residues (serine, cysteine, threonine);
 - 10 (4) small aliphatic residues (alanine, glycine); and
 - (5) proline.
110. The method of claim any one of 107-109, wherein the subject is human and the random
copolymer is administered at a daily dose of about 22mg per m² of the body surface area
of the subject.
- 15 111. The method of claim 107-109, wherein the subject is human and the random copolymer
is administered at a weekly dose of about 500mg per m² of the body surface area of the
subject.
112. The method of claim 107-109, wherein the subject is human and the random copolymer
is administered at a maximum dose of 500mg at time intervals greater than 4 days.
- 20 113. A method of treating a disease that is treatable with a random copolymer comprising
administering a composition comprising YEAk (L-tyrosine, L-glutamate, L-alanine and
L-lysine), synthesized by solid phase chemistry, in an input molar ratio of about 1.0: 2.0:
>6.0>15: 5.0 respectively by administering to a subject a dose effective in ameliorating
said diseases.
- 25 114. A kit comprising a premeasured injectable vial containing a composition comprising a
random copolymer YFAk and a pharmaceutically acceptable excipient.

115. A kit comprising a premeasured injectable vial containing a composition comprising a random copolymer selected from the group consisting of VYAK; VWAK; VEAk; FEAK; VAK; WAK; YAK; FAK; YEK; ELSA; DLYV; and KEASV and a pharmaceutically acceptable excipient.
- 5
116. A kit comprising a premeasured injectable vial containing a composition comprising a random copolymer wherein said random copolymer comprises a plurality of amino acid residues selected from:
- (1) hydrophobic, aliphatic residues (leucine, isoleucine, valine, methionine);
 - 10 (2) acidic residues (aspartic acid, glutamic acid);
 - (3) small hydrophilic residues (serine, cysteine, threonine);
 - (4) small aliphatic residues (alanine, glycine); and
 - (5) proline;
- and a pharmaceutically acceptable excipient.
- 15
117. The kit of claim 114, wherein the autoimmune disease is selected from the group consisting of multiple sclerosis, type-I diabetes, Hashimoto's thyroiditis, Crohn's disease, rheumatoid arthritis, systemic lupus erythematosus (SLE), gastritis, autoimmune hepatitis, hemolytic anemia, autoimmune hemophilia, autoimmune lymphoproliferative syndrome (ALPS), autoimmune uveoretinitis, glomerulonephritis, Guillain-Barré syndrome, psoriasis, myasthenia gravis, autoimmune encephalomyelitis, Goodpasture's syndrome, Grave's disease, paraneoplastic pemphigus, autoimmune thrombocytopenic purpura, scleroderma with anti-collagen antibodies, mixed connective tissue disease, pernicious anemia, polymyositis, idiopathic Addison's disease, autoimmune-associated infertility, bullous pemphigoid, Sjogren's syndrome, idiopathic myxedema and colitis.
- 20
- 25
118. The kit of claim 114, wherein the disease is an autoimmune disease.
119. The kit of claim 114, wherein the disease is multiple sclerosis.

120. The kit of claim 114, wherein the multiple sclerosis is relapsing-remitting multiple sclerosis
121. The kit of claim 114, wherein the disease is mediated by T_H1 cells.
- 5 122. A method for conducting a pharmaceutical business, comprising marketing the kit according to any one of claims 106-121 to healthcare providers the benefits of using the kit in the treatment of a disease or disorder.
123. A method for conducting a pharmaceutical business, comprising:
- (a) manufacturing the kit according to any one of claims 106-121; and
 - (b) marketing to healthcare providers the benefits of using the kit in the treatment
- 10 of a disease or disorder.
124. A method for treating a disease treatable by administering random copolymer comprising administering to a subject in need thereof a dosing regimen, wherein the random copolymer comprises YEAK (L-tyrosine, L-glutamate, L-alanine and L-lysine) in an output average molar ratio of about 1.0:2.0: 6.0: 5.0 respectively, synthesized by solid
- 15 phase chemistry, has a length of 52 amino acids, and wherein residues 1-10 of the copolymer sequence has a ratio of about 1.0:2.0: 5.5: 5.0, residues 11-30 have a ratio of about 1.0: 2.0: 6.0: 5.0, and residues 31-52 have a ratio of about 1.0: 2.0: 6.5: 5.0, wherein the dosing regimen inhibits formation of antibodies against the random copolymer.
- 20 125. A method for treating a disease treatable by administering random copolymer comprising administering to a subject in need thereof a dosing regimen, wherein the random copolymer is selected from the group consisting of VYAK; VWAK; VEAk; FEAK; VAK; WAK; YAK; FAK; YEK; ELSA; DLYV; and KEASV, wherein the dosing regimen inhibits formation of antibodies against the random copolymer.
- 25 126. A method for treating a disease treatable by administering random copolymer comprising administering to a subject in need thereof a dosing regimen, wherein the random copolymer comprises a plurality of amino acid residues selected from:

- (1) hydrophobic, aliphatic residues (leucine, isoleucine, valine, methionine);
- (2) acidic residues (aspartic acid, glutamic acid);
- (3) small hydrophilic residues (serine, cysteine, threonine);
- (4) small aliphatic residues (alanine, glycine); and
- 5 (5) proline. ;

wherein the dosing regimen inhibits formation of antibodies against the random copolymer.

- 127. The method of claim 124, 125, or 126, wherein said method induces peripheral tolerance in the subject to said random copolymer.
- 10 128. The method of claim 124, 125, 126, wherein said method induces central tolerance in the subject to said random copolymers.
- 129. A pharmaceutical composition comprising a random copolymer in a form of microparticles or emulsion.
- 130. The pharmaceutical composition of claim 129, wherein the random copolymer is in
15 aqueous phase, oil, and emulsifier, wherein the aqueous phase forms an water-in-oil emulsion.
- 131. The pharmaceutical composition of claim 129, wherein the random copolymer is suspended in alum.
- 132. The pharmaceutical composition of claim 130, wherein the oil is mineral oil and the
20 emulsifier is sorbitol monolaurate.
- 133. The pharmaceutical composition of claim 129, 130, 131, or 132, wherein the random copolymer is YEAK (L-tyrosine, L-glutamate, L-alanine and L-lysine), synthesized by solid phase chemistry, in an input molar ratio of about 1.0: 2.0: 6.0: 5.0 respectively.

134. The pharmaceutical composition of claim 129, 130, 131, or 132, wherein the random copolymer is selected from the group consisting of VYAK; VWAK; VEAK; FEAK; VAK; WAK; YAK; FAK; YEK; ELSA; DLYV; and KEASV.
- 5 135. The pharmaceutical composition of claim 129, 130, 131, or 132, wherein the random copolymer comprises a plurality of amino acid residues selected from:
- (1) hydrophobic, aliphatic residues (leucine, isoleucine, valine, methionine);
 - (2) acidic residues (aspartic acid, glutamic acid);
 - (3) small hydrophilic residues (serine, cysteine, threonine);
 - 10 (4) small aliphatic residues (alanine, glycine); and
 - (5) proline.

Figure 1
CO-14 efficacy in EAE: disease progression

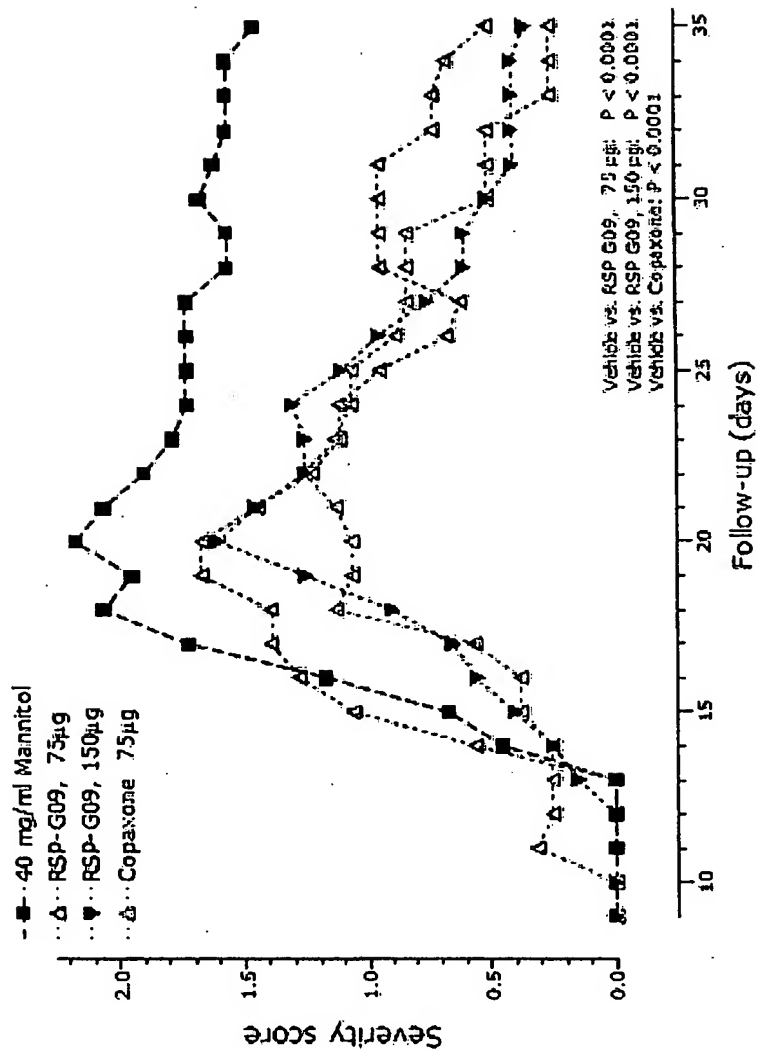


Figure 2
Efficacy in EAE: Survival proportions

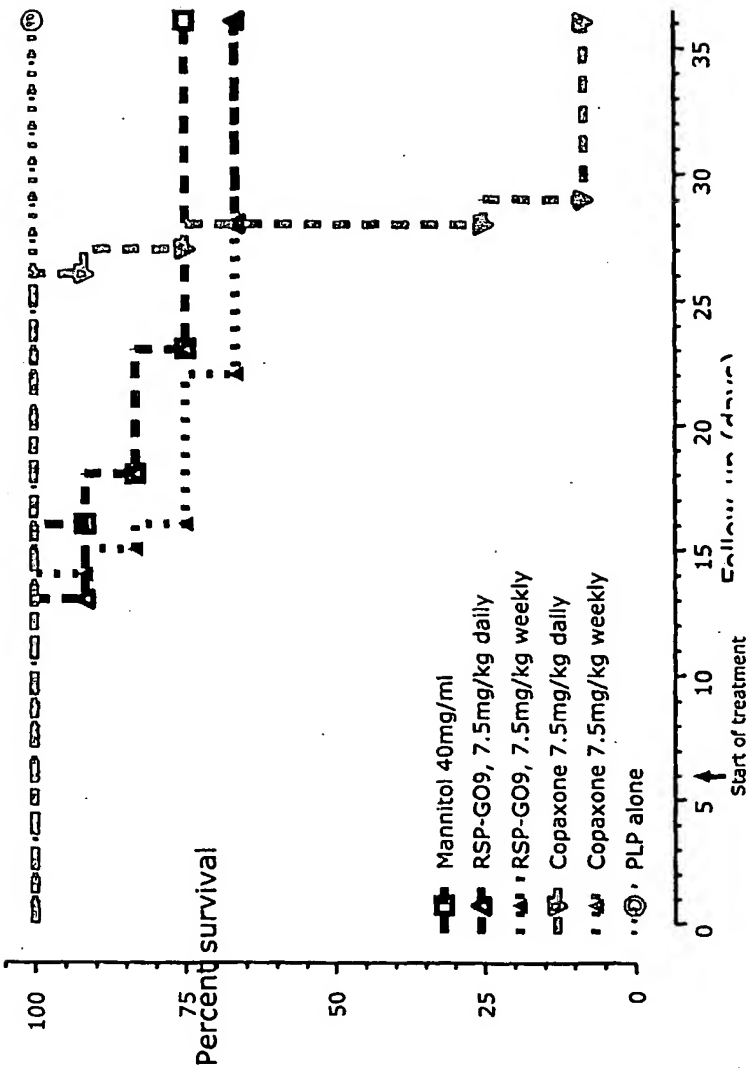


Figure 3

Antibody response against respective Copolymers

- total Ig ELISA, day 37 -

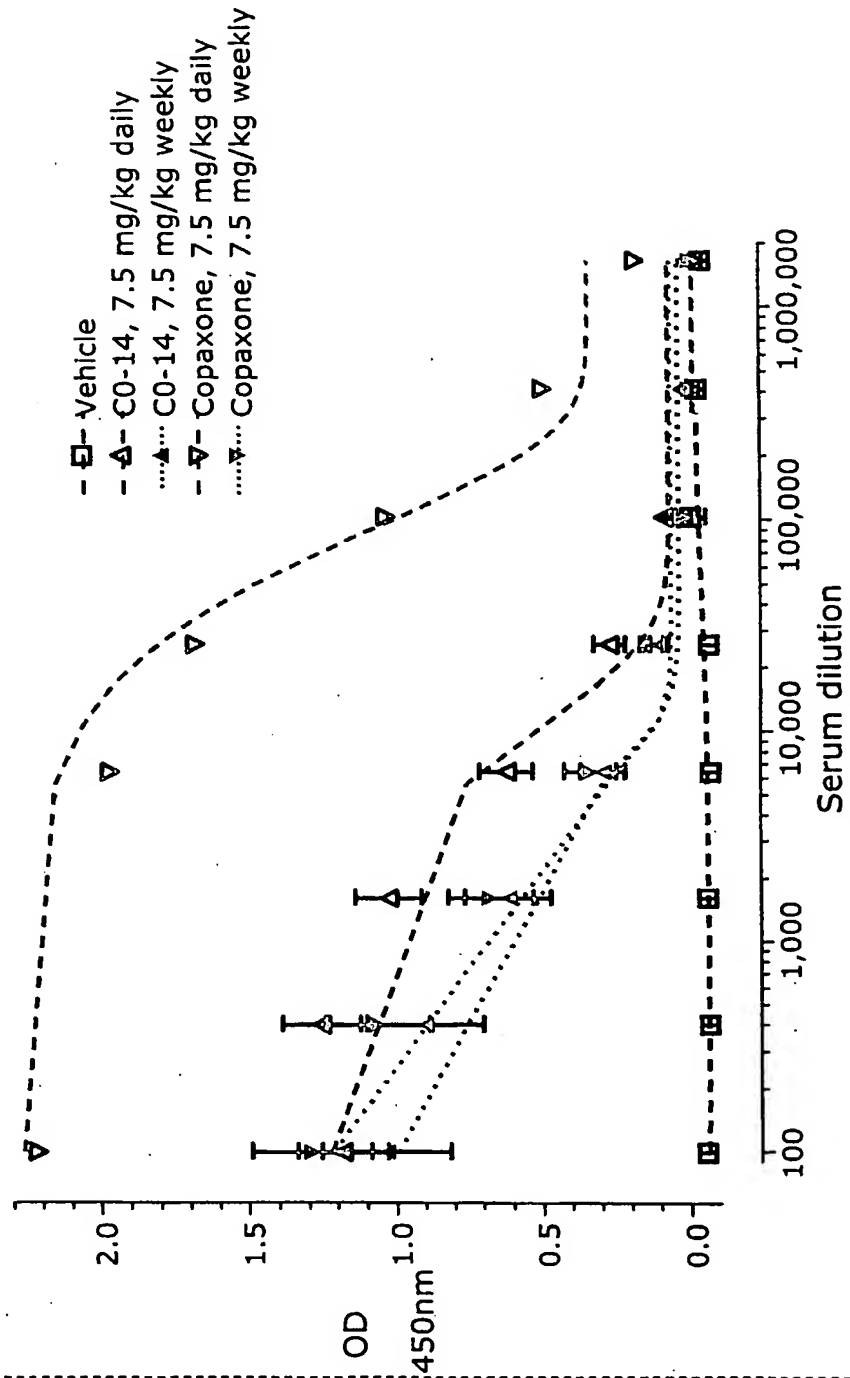


Figure 4
Antibody response against respective Copolymers
 - IgG1 ELISA, day 37 -

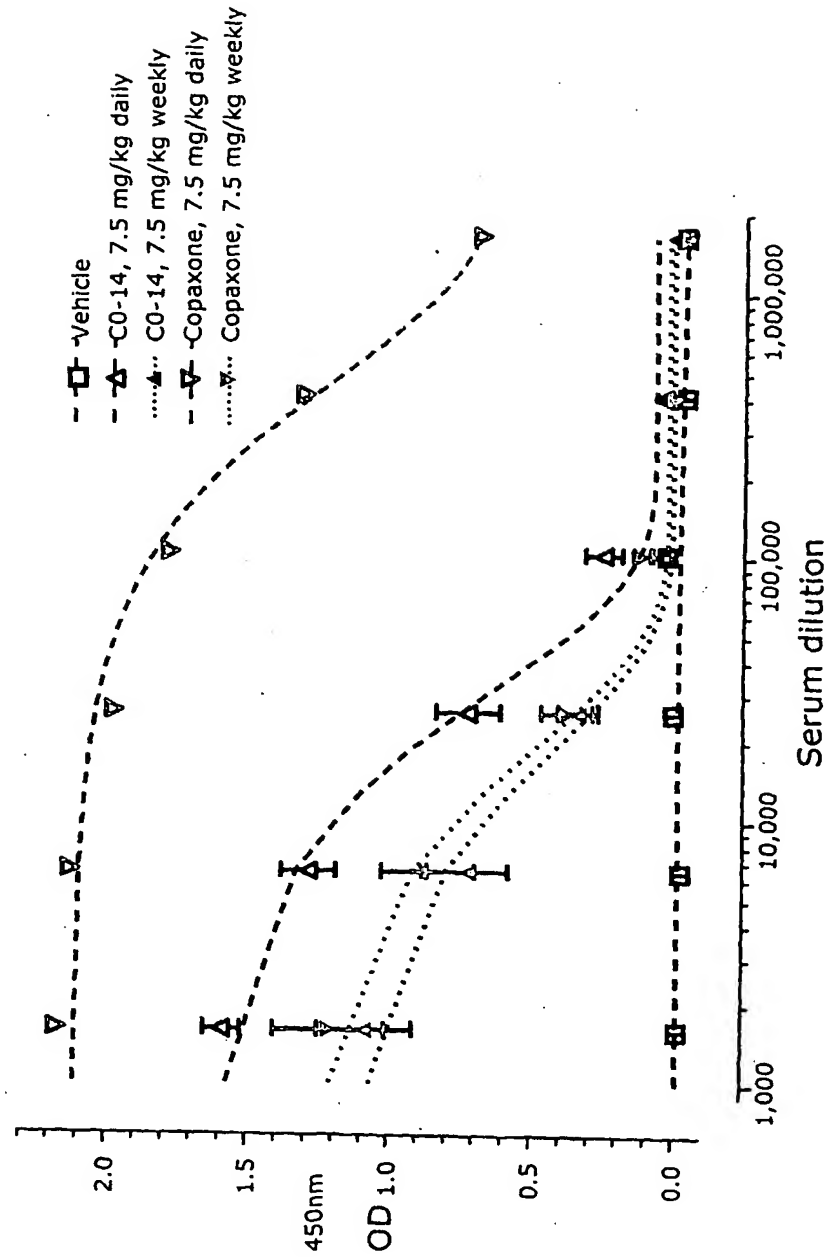


Figure 5
Antibody response against respective Copolymers
 - IgG2b ELISA, day 37 -

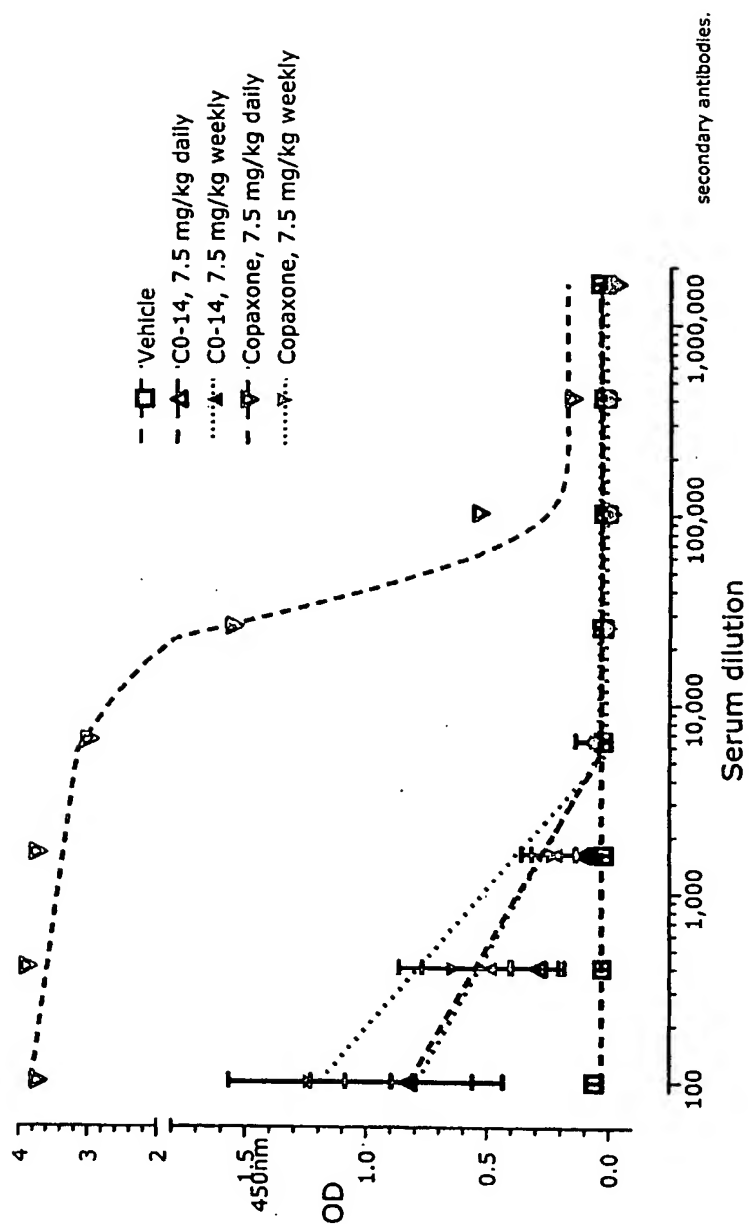


Figure 6

Changes in antibody (IgG) titers against relevant compounds during the course of treatment

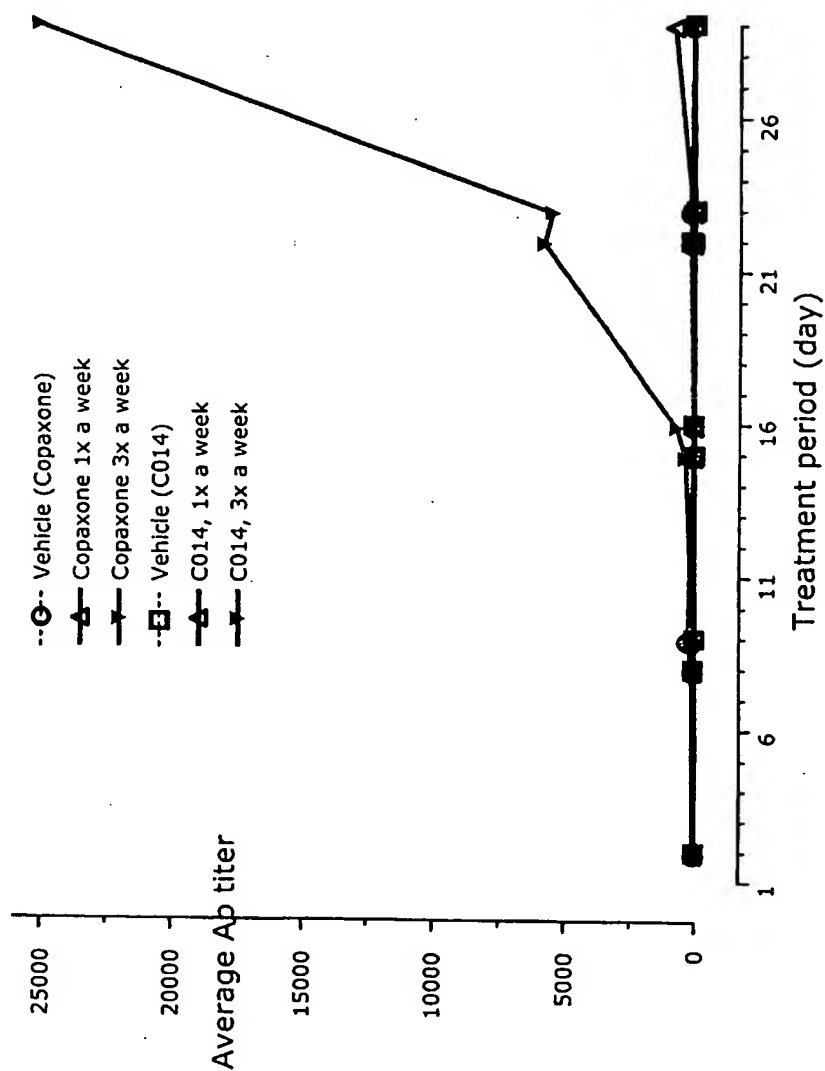


Figure 7
Antibody response against
autoantigen PLP(139-151)
 - IgG1 ELISA, day 37 -

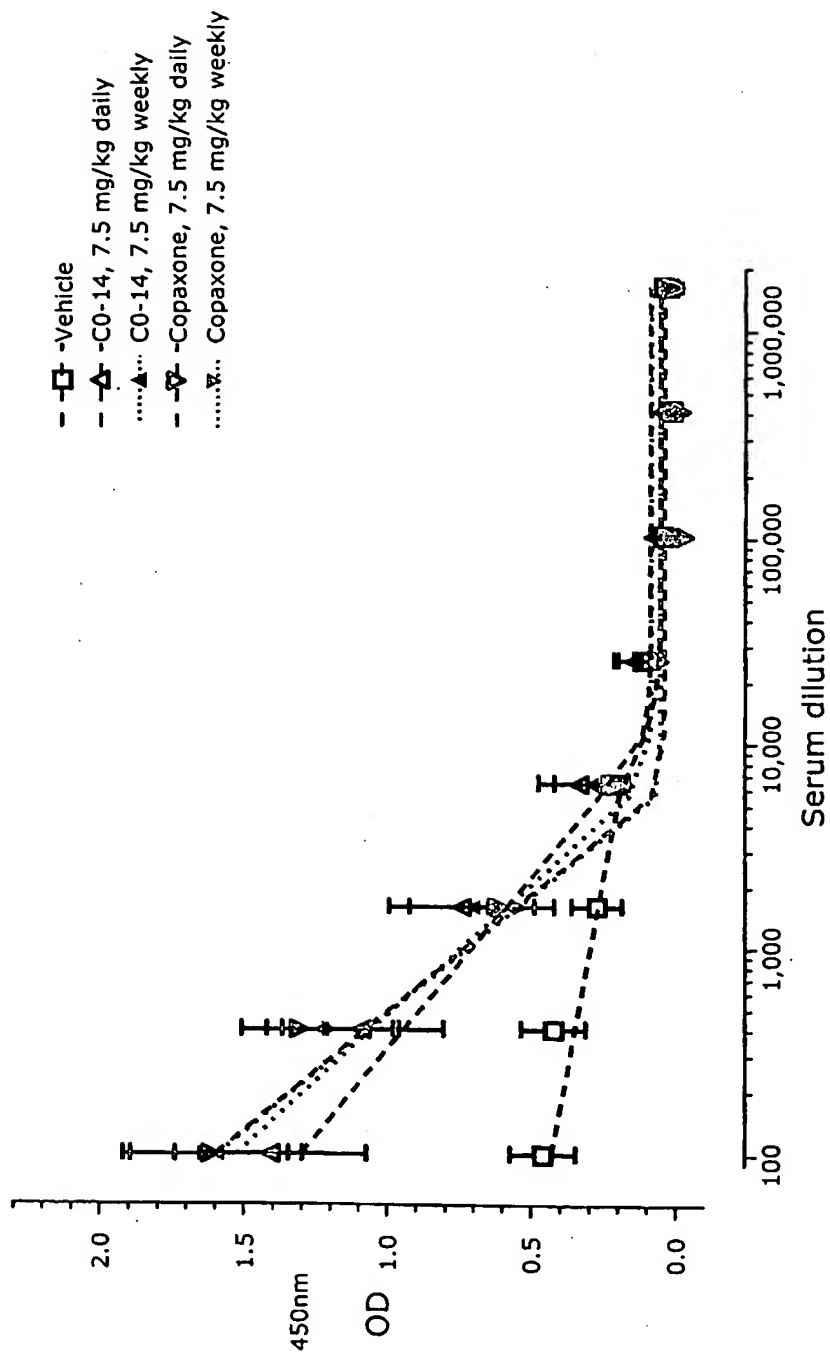


Figure 8

**Antibody response against
autoantigen PLP(139-151)**
- IgG2b ELISA, day 37 -

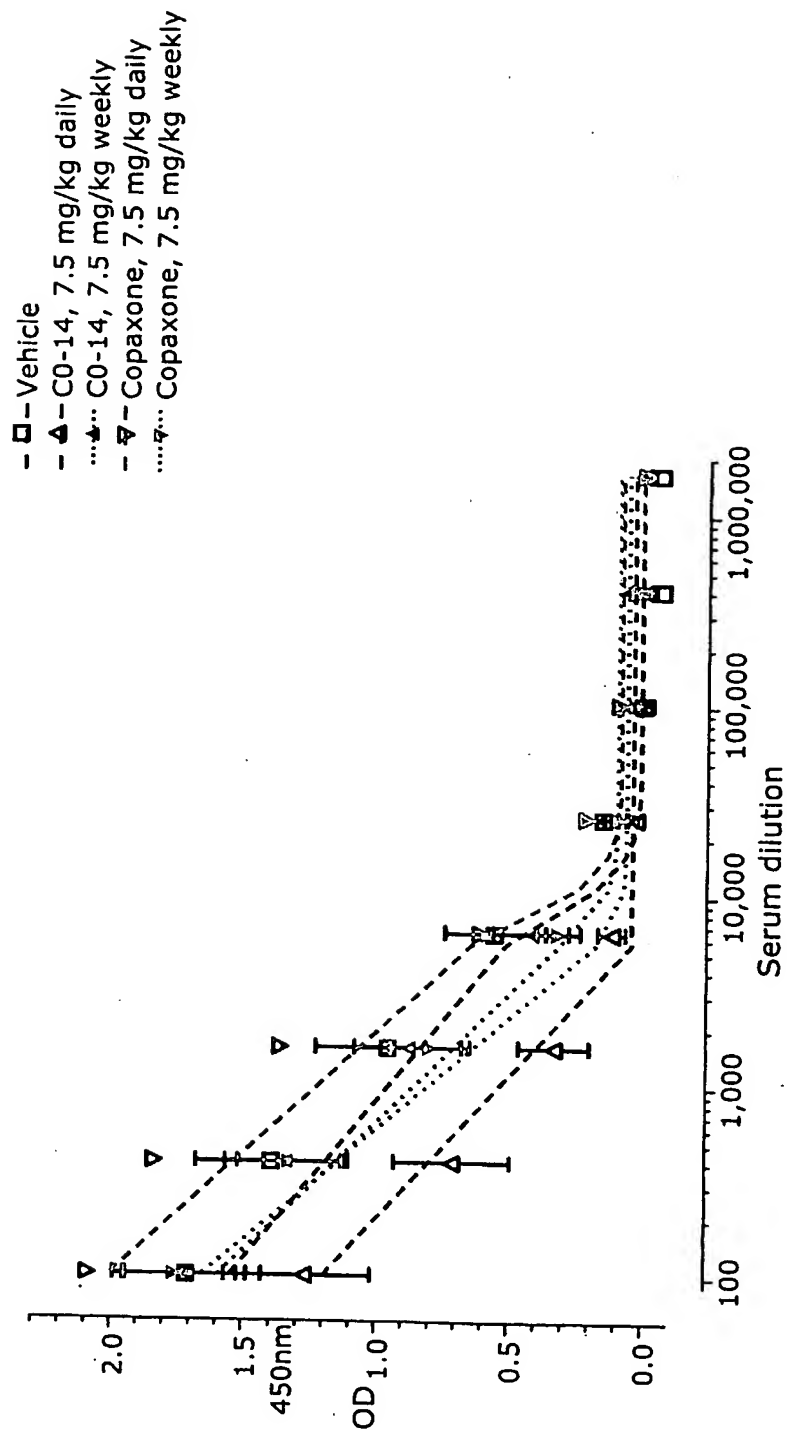


Figure 9

IT#6: IL-13/IFN γ ratio over treatment period
 - Response against 0.8 μ g/ml C014 or Copaxone with 2×10^5 cells/well -

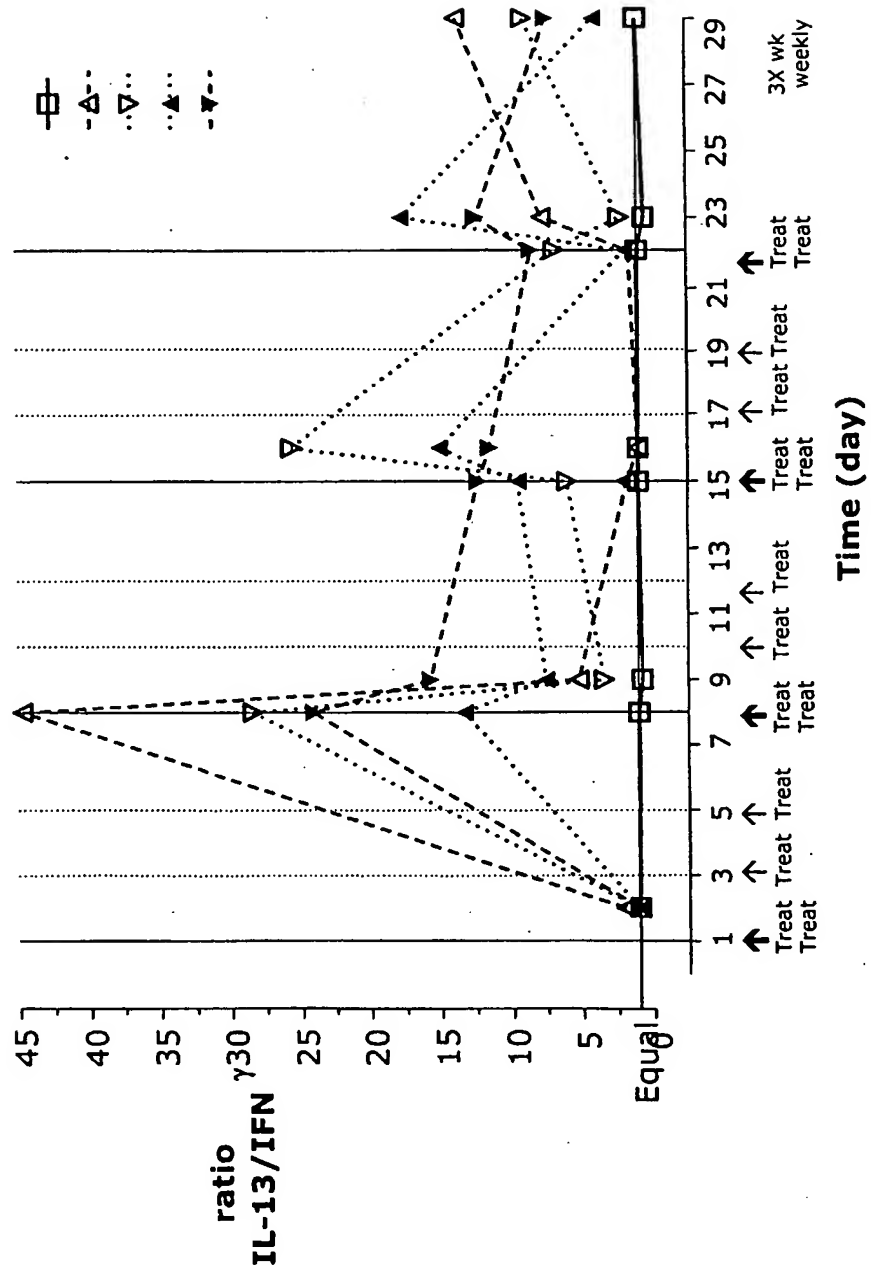
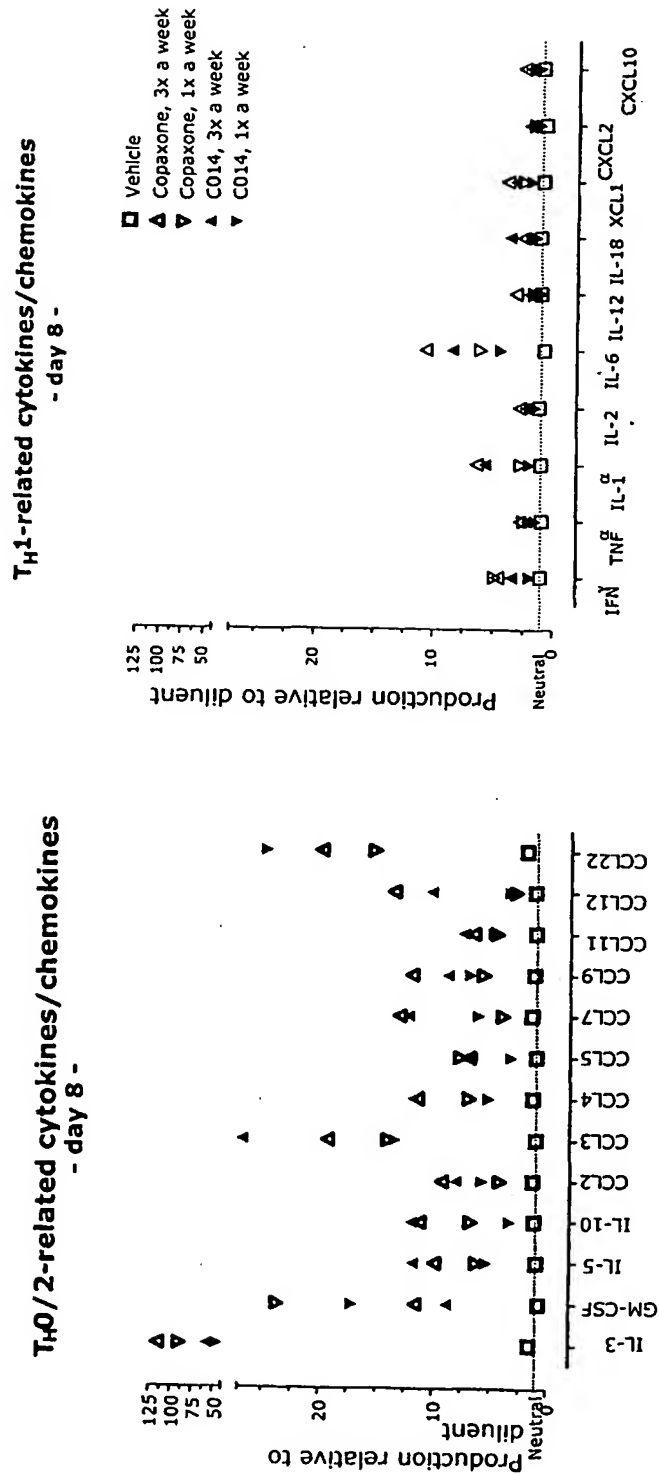


Figure 10



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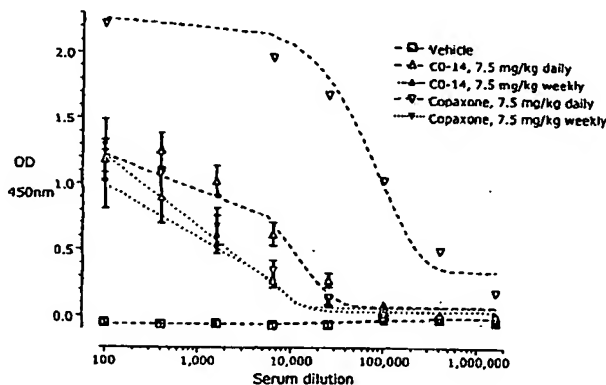
— with international search report
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(88) Date of publication of the international search report:
26 May 2006

[Continued on next page]

(54) Title: METHODS OF TREATING DISEASE WITH RANDOM COPOLYMERS

Antibody response against respective Copolymers
- total Ig ELISA, day 37 -



(57) Abstract: The invention relates to novel methods and kits for treating or preventing disease through the administration of random copolymers. The invention also relates to the treatment of autoimmune diseases, such as multiple sclerosis, and to the administration of random copolymers in treatment regimen comprising formulations that are administered at intervals greater than 24 hours, or to sustained release formulations which administer the copolymer over a period greater than 24 hours. The invention further relates to methods for conducting a pharmaceutical business comprising manufacturing, licensing, or distributing kits containing or relating to the formulations or dosing regimens of random copolymer described herein.

WO 2005/120542 A3



For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

INTERNATIONAL SEARCH REPORT

Application No
PCT/US2005/016340

A. CLASSIFICATION OF SUBJECT MATTER
A61K38/02 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K ---A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2003/004099 A1 (EISENBACH-SCHWARTZ MICHAEL ET AL) 2 January 2003 (2003-01-02) cited in the application paragraph '0091! - paragraph '0097!; examples paragraph '0110! - paragraph '0116!	1,4-98, 101, 104-107, 110-113, 124, 127-133
X	WO 00/27417 A (YEDA RESEARCH AND DEVELOPMENT CO. LTD; MCINNIS, PATRICIA, A; AHARONI,) 18 May 2000 (2000-05-18) cited in the application examples ----- -/--	1,4-98, 101, 104-107, 110-113, 124, 127-133

☒ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

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Date of the actual completion of the international search

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Date of mailing of the international search report

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3

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/016340

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FRIDKIS-HARELI MASHA ET AL: "Novel synthetic amino acid copolymers that inhibit autoantigen-specific T cell responses and suppress experimental autoimmune encephalomyelitis." THE JOURNAL OF CLINICAL INVESTIGATION. JUN 2002, vol. 109, no. 12, June 2002 (2002-06), pages 1635-1643, XP002311466 ISSN: 0021-9738 page 1636; table 1	1,2, 4-99, 101,102, 104-108, 110-113, 115, 122-125, 127-134
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	claims 25,27,34-50; figures; examples	
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	page 10, line 4; claims	
	----- -/-	

INTERNATIONAL SEARCH REPORT

national application No

PCT/US2005/016340

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>WO 03/047500 A (YEDA RESEARCH AND DEVELOPMENT CO. LTD; EISENBACH-SCHWARTZ, MICHAL; YOL) 12 June 2003 (2003-06-12)</p> <p>page 14, line 28 - page 15, line 4; claims</p>	<p>2,4-72, 99,102, 104-106, 108, 110-113, 115,122, 123,125, 129-132, 134</p>

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/016340

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-113 and 124-128 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
1, 2(part), 4-72(part), 73-98, 99(part), 101, 102(part), 104-106(part), 107
108(part), 110-113(part), 115(part), 122-123(part), 124, 125(part), 127, 128
129-132(part), 133, 134(part)
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows: - - -

1. claims:

1,4-72(part),73-98,101,104-106(part),
107,110-113(part),124,127,128,
129-132(part),133

A method of treating a treatable disease with a random YEAK copolymer and pharmaceutical compositions thereof.

2. claims:

2,4-72,99,102,104-106,108,110-113,115,
122-123,125,129-132,134(part)

A method of treating a treatable disease with a random VYAK copolymer and pharmaceutical compositions thereof.

3. claims:

2,4-72,99,102,104-106,108,110-113,115,
122-123,125,129-132,134(part)

A method of treating a treatable disease with a random VWAK copolymer and pharmaceutical compositions thereof.

4. claims:

2,4-72,99,102,104-106,108,110-113,115,
122-123,125,129-132,134(part)

A method of treating a treatable disease with a random VEAK copolymer and pharmaceutical compositions thereof.

5. claims:

2,4-72,99,102,104-106,108,110-113,115,
122-123,125,129-132,134(part)

A method of treating a treatable disease with a random FEAK copolymer and pharmaceutical compositions thereof.

6. claims:

2,4-72,99,102,104-106,108,110-113,115,
122-123,125,129-132,134(part)

A method of treating a treatable disease with a random VAK copolymer and pharmaceutical compositions thereof.

7. claims:

2,4-72,99,102,104-106,108,110-113,115,
122-123,125,129-132,134(part)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

A method of treating a treatable disease with a random WAK copolymer and pharmaceutical compositions thereof.

8. claims:

2,4-72,99,102,104-106,108,110-113,115,
122-123,125,129-132,134(part)

A method of treating a treatable disease with a random YAK copolymer and pharmaceutical compositions thereof.

9. claims:

2,4-72,99,102,104-106,108,110-113,115,
122-123,125,129-132,134(part)

A method of treating a treatable disease with a random FAK copolymer and pharmaceutical compositions thereof.

10. claims:

2,4-72,99,102,104-106,108,110-113,115,
122-123,125,129-132,134(part)

A method of treating a treatable disease with a random YEK copolymer and pharmaceutical compositions thereof.

11. claims:

2,4-72,99,102,104-106,108,110-113,115,
122-123,125,129-132,134(part)

A method of treating a treatable disease with a random ELSA copolymer and pharmaceutical compositions thereof.

12. claims:

2,4-72,99,102,104-106,108,110-113,115,
122-123,125,129-132,134(part)

A method of treating a treatable disease with a random DLYV copolymer and pharmaceutical compositions thereof.

13. claims:

2,4-72,99,102,104-106,108,110-113,115,
122-123,125,129-132,134(part)

A method of treating a treatable disease with a random KEASV copolymer and pharmaceutical compositions thereof.

14. claims:

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

3,4-72(part),100,103,104-106(part),
109,110-113(part),116,122-123(pa-
rt),126,129-132(part),135

A method of treating a treatable disease with a random
copolymer with a plurality of residues and pharmaceutical
compositions thereof.

15. claims: 114,117-121

A kit comprising a random copolymer YFAK.

INTERNATIONAL SEARCH REPORT

 International application No
 PCT/US2005/016340

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